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Review

The rise of food allergy: Environmental factors and emerging treatments

Sara Benedé [1], Ana Belen Blázquez [1], David Chiang [1], Leticia Tordesillas [1], M. Cecilia Berin *

Jaffe Food Allergy Institute, Immunology Institute, Mindich Child Health Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

Food allergy has rapidly increased in prevalence, suggesting an important role for environmental factors in disease susceptibility. The immune response of food allergy is characterized by IgE production, and new findings from mouse and human studies indicate an important role of the cytokine IL-9, which is derived from both T cells and mast cells, in disease manifestations. Emerging evidence suggests that route of exposure to food, particularly peanut, is important. Exposure through the skin promotes sensitization while early exposure through the gastrointestinal tract promotes tolerance. Evidence from mouse studies indicate a role of the microbiome in development of food allergy, which is supported by correlative human studies showing a dysbiosis in food allergy. There is no approved treatment for food allergy, but emerging therapies are focused on allergen immunotherapy to provide desensitization, while pre-clinical studies are focused on using adjuvants or novel delivery approaches to improve efficacy and safety of immunotherapy.

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1. Introduction

Food allergy is defined as "*an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food*" (Boyce et al., 2010) or as "*an adverse reaction to food in which immunologic mechanisms have been demonstrated*" (Muraro et al., 2014). This definition includes acute IgE-mediated type-I hypersensitivity reactions, such as hives, wheezing, or vomiting after exposure to common allergens such as peanut, milk, or egg. In addition, there are non-IgE-mediated food allergies that are characterized by delayed gastrointestinal reactions to foods, such as food protein induced enterocolitis syndrome (FPIES) or proctocolitis. Eosinophilic gastrointestinal disorders (EGID) are also commonly triggered by foods. This review will focus

* Corresponding author at: Department of Pediatrics, Box 1198, One Gustave L. Levy Place, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
E-mail address: cecilia.berin@mssm.edu (M.C. Berin).
[1] Equal contribution of authorship.

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on IgE-mediated food allergy, which is the most common and best-understood category of food allergy. Readers are referred to recent reviews on the pathophysiology of FPIES (Berin, 2015) or EGID (Rothenberg, 2015). (See Table 1.)

Food allergy is increasing in prevalence (Savage and Johns, 2015) for reasons that are not yet clear. A rigorous population-based study utilizing food challenges to demonstrate food allergy showed that approximately one in 10 Australian children had a food allergy at one year of age (Osborne et al., 2011). Estimates in the US and Canada indicate a prevalence rate of 1 in 15 to 1 in 20 (Soller et al., 2012; Sicherer and Sampson, 2014). Factors such as hygiene and lack of exposure to microbial factors, composition of the intestinal microbiota, diet, obesity, Vitamin D, and environmental chemical exposure have all been proposed to contribute to this alarming rise in the rate of food allergy in countries with a Westernized lifestyle. This review will review recent advances in our understanding of the pathophysiology of food allergy, and identify new approaches for the treatment of food allergy.

2. Mechanism of anaphylaxis

IgE-mediated food allergy is triggered by allergen cross-linking of IgE bound to the surface of mast cells or basophils, as in a typical type I hypersensitivity reaction. The most severe manifestation of food allergy is anaphylaxis, which is an acute reaction affecting 2 or more organ systems that can be life threatening (Kim and Fischer, 2011; Muraro et al., 2014; Simons and Sampson, 2015). Although IgE-mediated activation of tissue mast cells and circulating basophils is thought to represent the major source of mediators that contribute to the pathology of anaphylaxis (Kalesnikoff and Galli, 2010), other cell types such as neutrophils and macrophages and other antibody isotypes such as IgG have been described to contribute to anaphylaxis (Jonsson et al., 2011; Tsujimura et al., 2008; Strait et al., 2002). The existence of these alternative pathways of anaphylaxis has not yet been described in humans.

Histamine correlates with anaphylaxis severity (Brown et al., 2013) and histamine receptor blockers are the first line treatment to relieve mild to moderate allergy symptoms. In addition, platelet-activating factor (PAF) shows a pivotal role as a mediator of anaphylaxis in mice (Arias et al., 2009) as well as in humans (Vadas et al., 2012), where levels correlate with anaphylaxis severity. PAF receptor antagonists, which inhibit the binding of PAF to the receptor, reduce mortality associated with anaphylaxis in animal models (Arias et al., 2009), and deficiency of PAF-AH (PAF acetylhydrolase), the enzyme that inactivates PAF, predisposed patients to severe anaphylaxis (Vadas et al., 2008), demonstrating the role of this pathway.

Table 1
Glossary of food allergy related terms.

Term	Definition
IgE-mediated food allergy	Adverse reaction to a food source mediated by the cross-linking of specific IgE bound to mast cells and basophils through FcεRI.
Non-IgE mediated food allergy	Adverse reaction to a food source that is not mediated by IgE. Symptoms are typically delayed (hours) and are thought to be cell mediated.
Anaphylaxis	Acute, systemic reaction that can occur within minutes of exposure and includes symptoms such as vomiting, skin rash, rapid and weak pulse, abdominal pain, swollen throat, trouble breathing or swallowing, diarrhea, chest tightness.
Sensitized	Having positive IgE to the allergen, with or without symptoms
Allergic	Sensitized individual with allergic symptoms to the allergen
Th2	T helper cells producing IL-4 and IL-13
Tfh	T helper cells homing to lymph node follicles (and identified as CXCR5+) and enabling B cell isotype switching
Treg	Regulatory T cell, mostly commonly a CD4+ T cell expressing the transcription factor Foxp3
Epithelial cytokines	TSLP, IL-33, IL-25 are epithelial-derived cytokines that can promote the generation of Th2 cells
Allergen-specific immunotherapy	Prolonged treatment consisting in the administration of increasing amount of a specific allergen to reduce symptoms. It can be applied by different routes:
SLIT	Sublingual immunotherapy: the allergen is given as drops under the tongue.
OIT	Oral immunotherapy: the allergen is administered orally.
EPIT	Epicutaneous immunotherapy: the antigen is applied on the skin using a patch or similar device.
Desensitization	Clinical non-responsiveness while antigen-specific immunotherapy is maintained
Clinical tolerance	Sustained clinical non-responsiveness to food allergen after discontinuation of therapy

3. Immune profile of food allergy

Despite the fact that IgE plays a central role in the pathogenesis of food allergy, measurement of food-specific IgE is not diagnostic in isolation. Quantification of food-specific IgE antibody levels in serum can identify patients in the pediatric population who are highly likely (>95%) to experience clinical reactions to egg, milk, peanut or fish, as recently reviewed (Chokshi and Sicherer, 2016). However lower levels poorly discriminate between those who are sensitized versus allergic. Detection of IgE reactivity against components of food (for example the protein allergen Ara h 2 in peanut or Cor a 14 for hazelnut) improves specificity (Klemans et al., 2015; Beyer et al., 2015; Eller and Bindslev-Jensen, 2013). Ara h 2 is digestion-resistant and can trigger systemic reactions while Ara h 8 is cross-reactive with birch pollen allergens (and can result in positive IgE to peanut in birch pollen-allergic individuals), is susceptible to digestion, and does not trigger systemic reactions. IgE levels against whole peanut extract would not discriminate between IgE to these two allergens with differing potential to trigger reactions. Antibody isotypes other than IgE, such as IgG and IgA, are not predictive of food allergy. However, ratio of egg white allergen-specific IgE/IgG4 has been shown to be better than IgE levels alone in predicting clinical reactivity to egg (Okamoto et al., 2012; Caubet et al., 2012).

For the production of IgE antibodies, B cells require help from allergen-specific T cells producing IL-4, either Th2 or T follicular helper (Tfh) cells. T cells from allergic patients display a uniquely Th2 cytokine production profile (Prussin et al., 2009). IL-9 production from a T cell subset distinct from those producing IL-5 was recently reported to differentiate between children with peanut allergy and children with peanut sensitization (Brough et al., 2014). In addition, it was recently reported in mice that a population of intestinal mast cells express IL-9, promote experimental food allergy in an IL-9-dependent manner, and are dependent on Th2 cells for their development (Chen et al., 2015). Furthermore, the authors showed that in patients with food allergy, duodenal biopsies had elevated expression of genes associated with the mast cell signature (IL-9, IL-13, chymase, and tryptase). Thus innate events in the intestinal tissue may be critical for linking systemic Th2-skewed adaptive responses to symptoms.

Food allergy is commonly referred to as a failure of oral tolerance, a systemic state of antigen-specific immune suppression that is mediated by regulatory T cells. However, there is little information on the role of Tregs in food allergy. In mouse models, administration of Tregs can suppress food allergy (Burton et al., 2014). Furthermore, in mice genetically susceptible to food allergy there is an impairment of Treg function, and evidence of Th2 reprogramming such that Tregs contribute to Th2 cytokine production rather than suppress it (Noval Rivas et al., 2015). This was also observed in peripheral blood of subjects with milk allergy (Noval Rivas et al., 2015), supporting the hypothesis that food allergy is a failure of regulatory T cells.

4. Emerging evidence for the role of the skin in food allergy

There is growing evidence pointing to the skin as the main site of sensitization to food allergens, particularly peanut. The majority of patients with peanut or tree nut allergy experienced their first reaction the first time that the food was knowingly ingested, so previous